PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
100925-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2003/001955	15.12.2003	17.12.2002
International Patent Classification (IPC) or national classification and IPC		
C07D 401/12, C07D 401/14, A61K 31/497, A61P 25/00, A61P 3/10, A61P 5/48, A61P 15/18, A61P 17/14		
Applicant		
AstraZeneca AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.06.2004	22.03.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/001955

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/001955

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 16-19

because:

☒ the said international application, or the said claims Nos. 16-19 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 8 and 10 are so unclear that no meaningful opinion could be formed *(specify)*:

The expression "conditions associated with glycogen synthase kinase-3" in claims 8 and 10 is not clear and concise and does not comply with PCT Articles 5 and 6 as it defines the conditions by the mechanism behind the conditions and does not mention the specific conditions. It is therefore not

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III.2

clear which conditions are comprised by these claims. The examination has been performed on the general expression in some parts but has mainly been focused on the conditions named in claims 11-14.

Box No. IV Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

- ☐ complied with.
- ☐ not complied with for the following reasons:

The compounds defined by the application have been divided into three inventions according to the following:

1) Compounds according to formula I. Pharmaceutical formulations, use and methods involving these compounds. Claims 1-4 and 7-19.

2) The compound 3-amino-6-bromo-N-pyridin-3-ylpyrazine-2-carboxamide and use of this compound. Claims 5 and 20 partially.

3) The compound N-[3-(4-bromophenyl)propyl]-N,N-dicyclobutylamine and use of this compound. Claims 6 and 20 partially.

Only invention 1 is examined.

4. Consequently, this report has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-4 and 7-19

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-4, 7-15	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-4, 7-15	NO
Industrial applicability (IA)	Claims	1-4, 7-15	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The following documents are cited in the search report:

D1 WO 0168612 A2
D2 US 2001/0031772 A
D3 WO 02092585 A1
D4 WO 0160806 A2
D5 US 6255307 B1

The claimed invention relates to novel pyridine/pyrazine-2-carboxamide derivatives, which have a selective inhibiting effect on glycogen synthase kinase 3 (GSK3) as well as a good bioavailability. The compounds can be used in the treatment of e.g. dementia, Alzheimer´s Disease, chronic neurodegenerative diseases or diabetes.

D1 discloses structurally close compounds, which can be used in the treatment of e.g. neurodegenerative and manic-depressive conditions. The claimed compounds differ from the known in the group R in this application.

D2 discloses structurally close compounds, which can be used in the treatment of diabetes. The claimed compounds differ from the known by the substitution on the aromatic ring (P in this application).

The problem to be solved regarding the state of the art is to prepare further compounds, which have a selective inhibiting effect on glycogen synthase kinase 3 (GSK3) and can be used in the treatment of e.g. dementia, Alzheimer´s Disease, chronic neurodegenerative diseases or diabetes. This has been achieved

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

by the structurally close compounds in D1 and D2.

Considering what is known from D1 and other prior art it is considered to lie within the skills of a person skilled in the art to prepare structurally close compounds which have a selective inhibiting effect on glycogen synthase kinase 3 (GSK3) and can be used in the treatment of e.g. dementia, Alzheimer's Disease, chronic neurodegenerative diseases or diabetes. As no other effect than the claimed has come out, the invention as defined in claims 1-4 and 7-15 lacks inventive step.

It is therefore considered to be obvious to a person skilled in the art to use the novel compounds of formula (I) in the treatment of glycogen synthase kinase 3 (GSK3) related diseases.

Claims 1-4 and 7-15 relate to a selection of compounds according to the general formula (I). Such a selection can only be considered as patentable if the novel compounds in the present patent application present an unexpected effect compared to the known compounds in the above cited documents.

D3-D5 disclose the general state of the art and are not considered to be particular relevant.

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 is not supported by the description as required by Article 6 PCT, as its scope is broader than justified by the description and examples. The reasons therefore are that the claims relate to an extremely large number of possible compounds and a complete examination over the whole scope is not possible.